

BRIEF REPORT

Use of Recombinant Factor VIIa (rFVIIa) to Control Intraoperative Bleeding in Pediatric Brain Tumor Patients

M. Heisel, MD,* M. Nagib, MD, L. Madsen, RN-CNP, M. Alshiekh, MBBS, and A. Bendel, MD

Surgical bleeding during the resection of brain tumors in children may be related to tumor vascularity, pathology, and location. Despite improvements in neurosurgical technique, neuroanesthesia, and blood product replacement, bleeding can be life-threatening in these surgeries. We report eight pediatric patients in whom recombinant factor VIIa (rFVIIa) was used to control intraoperative bleeding during surgical

resection of pediatric brain tumors. rFVIIa should be considered as a method to control intraoperative bleeding that is unresponsive to conventional interventions. Additional studies are needed to determine optimal patient selection and drug dosing, efficacy and safety. *Pediatr Blood Cancer* 2004;43:703–705. © 2004 Wiley-Liss, Inc.

Key words: pediatric; recombinant factor VIIa; rFVIIa; surgical hemostasis

INTRODUCTION

Brain tumors are the most common solid tumors of childhood [1,2]. Tumor resection is a standard treatment option, but one that may be complicated by significant blood loss due to tumor pathology, location, and/or vascularity. Survival rates for children with brain tumors have greatly improved with advances in neurosurgical techniques and neuro-anesthesia. Despite these advances, intraoperative blood loss continues to be a serious medical problem for some patients.

Recombinant factor VIIa (NovoSeven[®], Novo Nordisk, Denmark) is a hemostatic agent developed for the treatment of bleeding episodes in hemophilia patients with high titer inhibitors [3]. It was approved for use in Europe in 1996 and FDA-approved in 1999 for the treatment of bleeding episodes in patients with hemophilia A or B with inhibitors. rFVIIa was subsequently used for patients with life-threatening hemorrhage associated with massive trauma [4], surgery [5], thrombasthenia (e.g. Glanzmann's) [6], congenital factor VII deficiency [7], acquired factor VIII inhibitors [8], liver failure [9], and other medical situations in which life-threatening hemorrhage was not responsive to conventional therapeutic interventions.

rFVIIa works through a unique mechanism of action, triggering the extrinsic pathway of the coagulation cascade by forming a complex with exposed tissue factor (TF) at the site of injury. This activated VIIa–TF complex causes the activation of factors IX and X and the ultimate production of thrombin at the site of injury, thus its effectiveness in treating surgical bleeding [10]. This report describes the utilization of rFVIIa to achieve intraoperative hemostasis in eight pediatric patients who

experienced massive bleeding during the neurosurgical resection of their brain tumors.

CASE REPORT

The patient was a 2-year-old female (see Table, Case 1) who presented with a 1-month history of intermittent vomiting, lethargy, and low-grade fever. Physical examination revealed frontal bossing and dilated scalp veins. The neurologic exam was nonfocal, although the child was quite irritable. Coagulation laboratory results were within normal limits. Magnetic resonance imaging demonstrated hydrocephalus and a large (7.1 × 6.1 × 6.9 cm) enhancing tumor arising from the left lateral ventricle.

The child underwent surgical resection through a left-sided frontal parietal craniotomy with intersulcal approach to the lateral ventricle. One hour and 45 minutes after surgical incision, the patient experienced massive bleeding. Coagulation laboratory results obtained as the bleeding began were as follows: PT = 11.5 sec; INR = 0.87; PTT = 27.9 sec; fibrinogen = 393 mg/dl; platelets = 401 × 10⁹/L. A blood loss of 5,000 cc (509 cc/kg) was replaced with a total of 5,000 cc of packed red

Children's Hospitals and Clinics, Department of Hematology/Oncology, Minneapolis and St. Paul, Minnesota

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*Correspondence to: Margaret Heisel, Children's Hospitals and Clinics, Hematology/Oncology Clinic, 2525 Chicago Ave. S; Suite 4150, Mailstop 32-4150, Minneapolis, MN 55404.
E-mail: Margaret.Heisel@childrenshc.org

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blood cells, platelets, fresh frozen plasma, and cryoprecipitate. Blood loss continued, and despite blood product replacement the patient was hemodynamically unstable. rFVIIa (120 mcg/kg) was administered intravenously and hemostasis was achieved within 30 min. Coagulation laboratory values after rFVIIa administration were as follows: PT = 12.5 sec; INR = 0.90; PTT = 102 sec; fibrinogen = 142 mg/dl; platelets = $251 \times 10^9/L$. The patient's clinical condition stabilized and successful resection of the tumor was achieved. There were no further intraoperative complications.

The child recovered without complications related to the surgical intervention, blood loss, or rFVIIa administration. Twenty-four hours after surgical resection the patient's coagulation values were as follows: PT = 11.8 sec; INR = 0.90; PTT = 27.9 sec; fibrinogen = 196 mg/dl; platelets = $223 \times 10^9/L$. Histopathology of the tumor revealed a choroid plexus carcinoma.

rFVIIa was subsequently administered to seven additional pediatric patients undergoing surgical resection of brain tumors. The patients are described in Table I. In all patients, rFVIIa was administered for what was considered abnormal bleeding at the time of surgery. In two patients (cases 3 and 8), the rFVIIa was administered in a manner similar to that for patient 1 (after major blood loss and with hemodynamic instability despite blood product replacement). In four patients, rFVIIa was administered earlier in the surgical procedure, when it was determined by the neurosurgeon that neurosurgical techniques would not control the bleeding. This earlier administration was at the discretion of the neurosurgeon.

DISCUSSION

In the past several years, rFVIIa has been used for certain platelet function disorders [11,12], congenital factor VII deficiency, and liver failure [7,9], as well as for patients with catastrophic bleeding associated with liver transplantation [13], cardiac surgery [14], trauma [4], and neurosurgical procedures [15]. These reports describe a remarkable response to rFVIIa, with control of life-

threatening bleeding that was not responsive to surgical intervention or conventional blood product replacement.

Any surgical procedure or trauma with catastrophic blood loss and resultant blood product replacement may cause coagulation abnormalities and impaired thrombin generation. rFVIIa provides a unique approach to the activation of the clotting system which enhances hemostasis. However, concerns have been raised about the risk of thrombosis in surgical procedures or trauma situations where rFVIIa is used and the clotting system has already been activated due to massive blood loss and hypotension. An additional concern is the use of rFVIIa in neurosurgical procedures where intraoperative release of tissue thromboplastin may cause additional activation of the clotting system. Special care must be taken with the use of rFVIIa in infants who may not have a mature and fully functional fibrinolytic system. The use of rFVIIa may place them at further risk of disseminated intravascular coagulation and thrombosis in these situations.

This report describes a series of pediatric neurosurgical patients (n = 8) who received rFVIIa for the treatment of potentially life-threatening blood loss during neurosurgery. In these patients, rFVIIa was administered to control intraoperative bleeding that failed to respond to standard neurosurgical techniques and blood product replacement. In all but one of these procedures, there was excellent response to rFVIIa, with control of bleeding and successful completion of the neurosurgical procedure. For one patient, although hemostasis was ultimately achieved, it could not be related specifically to the administration of rFVIIa (case 3). The reason for the failure of rFVIIa to control bleeding during this procedure is unknown. Two patients required multiple doses of rFVIIa to attain hemostasis (cases 7 and 8). These doses were administered at approximately 20–30 min intervals, when it was obvious that the bleeding was not being controlled by rFVIIa, neurosurgical techniques, or blood product replacement.

Three of the patients received rFVIIa when they experienced massive blood loss (140–500 cc/kg) during a surgical procedure. Five other patients received it earlier in their surgical procedures, when the blood loss was

TABLE I. Clinical Features of Eight Pediatric Patients Who Received rFVIIa

ID #	Age: (months)	Diagnosis	Blood loss (cc/kg)	rFVIIa administered (mcg/kg)	Hemostasis?
1	24	Choroid plexus carcinoma	509	120	Yes
2	204	High-grade glioma	5	275	Yes
3	3	Meningeal sarcoma	140	98: two doses	No
4	156	Anaplastic oligodendroglioma	30	102	Yes
5	31	Grade 1 pilocytic astrocytoma	20	75	Yes
6	57	Medulloblastoma	20	86	Yes
7	3	Pineal region tumor	30	90: two doses	1st dose: no 2nd dose: yes
8	58	Giant tentorial meningioma	200	1st and 2nd dose ~115; 3rd dose = 220	1st 2nd dose: no 3rd dose: yes

felt by the neurosurgeon to be uncontrolled by surgical techniques. Blood product support was ongoing in these cases but it was the neurosurgeon's decision to administer rFVIIa before massive blood loss occurred. It is possible that with the use of additional neurosurgical techniques and ongoing blood product replacement, this massive blood loss might have been controlled without the use of rFVIIa. However, although substantial concerns existed about the cost of rFVIIa and its potential for adverse events, such concerns were offset by the potential for life-threatening blood loss with resultant massive transfusion exposure and postoperative complications related to hemodynamic instability.

rFVIIa was successfully used in pediatric neurosurgical patients to control intraoperative bleeding. The rFVIIa was well tolerated and resulted in no obvious adverse effects. However, the risk of disseminated intravascular coagulation and thrombosis must be recognized in young children receiving this product, particularly infants with an immature fibrinolytic system. As observed in our case 3, rFVIIa administration is not always effective in achieving hemostasis. Factors to be considered are the dosing of rFVIIa, the timing of intervention, and possible unknown underlying medical or surgical conditions. Additional studies are warranted to assess patient selection, optimal dosing, drug efficacy, and drug safety. The development of a protocol is recommended for the use of rFVIIa in neurosurgical patients who experience catastrophic blood loss to address these concerns.

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